

# United States Patent Application for:

## Increased Dosage Metered Dose Inhaler

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Docket No.: 0150.00

### CERTIFICATE OF EXPRESS MAILING:

"Express Mail" mailing label number ER212309792US Date of Deposit October 30, 2003

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

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## Increased Dosage Metered Dose Inhaler

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/422,563, filed on October 30, 2002, which is incorporated herein by reference in its entirety.

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### BACKGROUND

The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, an aerosolized pharmaceutical formulation provides local therapeutic relief to a portion of the respiratory tract, such as the lungs, to treat diseases such as asthma and emphysema. In another inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of aerosolization devices exist including devices comprising a pharmaceutical formulation stored in or with a propellant, devices that aerosolize a dry powder, devices which use a compressed gas to aerosolize a liquid pharmaceutical formulation, and similar devices.

One conventional type of aerosolization device is commonly referred to as a metered dose inhaler (MDI), which is sometimes referred to as a pressurized metered dose inhaler (pMDI). In a metered dose inhaler, a pharmaceutical formulation and a propellant are stored in a canister. In one version the pharmaceutical formulation is suspended within the propellant, and in another version the pharmaceutical formulation is dissolved in the propellant. In either version, a valve may be actuated so that a metered amount, or dose, of the pharmaceutical formulation is aerosolized in a manner where it may be inhaled by a user. The canister may contain one or more doses of the pharmaceutical formulation and generally contains sufficient amounts of propellant to

allow for several actuations. Traditionally, the propellant comprises one or more chlorofluorocarbon compounds. However, non-chlorinated propellants, such as hydrofluoroalkanes, that are believed to be more environmentally friendly are proving to be a desirable alternative.

Though generally well accepted and inexpensive, metered dose inhalers have certain drawbacks. For example, the amount of pharmaceutical formulation that may be aerosolized during an actuation is limited. In addition, it can often be difficult to control the efficiency of delivering large quantities of a pharmaceutical formulation using a metered dose inhaler.

Therefore, it is desirable to be able to aerosolize a pharmaceutical formulation in an efficient manner. It is further desirable to provide an improved metered dose inhaler that is capable of effectively aerosolizing a large quantity of a pharmaceutical formulation. It is still further desirable to provide an improved metered dose inhaler with improved aerosolization efficiency and reproducibility.

### SUMMARY

The present invention satisfies these needs. In one aspect of the invention a large and/or uniform aerosol dose of medicament is delivered from a metered dose inhaler.

In another aspect of the invention, an aerosolization apparatus comprises a container containing a pharmaceutical formulation, the pharmaceutical formulation comprising an active agent and a propellant; a metering chamber in communication with the container, the metering chamber adapted to hold a metered amount of the pharmaceutical formulation; a valve to allow the metered amount of the pharmaceutical formulation to be released from the metering chamber when the valve is actuated; and a pressurizer that applies pressure to the pharmaceutical formulation in the metering chamber while the pharmaceutical formulation is being released from the metering chamber, wherein the metering chamber is sized so that at least 2 mg of the active agent is be aerosolized for delivery to a user during inhalation.

In another aspect of the invention, an aerosolization apparatus comprises a container containing a pharmaceutical formulation, the pharmaceutical formulation comprising an active agent and a propellant; a metering chamber in communication with the container, the metering chamber having a metering volume of at least 150  $\mu$ l and being adapted to hold a metered amount of the pharmaceutical formulation; a valve to allow the metered amount of the pharmaceutical formulation to be released from the metering chamber when the valve is actuated; and a pressurizer that applies pressure to the pharmaceutical formulation in the metering chamber while the pharmaceutical formulation is being released from the metering chamber.

In another aspect of the invention, an aerosolization apparatus comprises a container containing a pharmaceutical formulation, the pharmaceutical formulation comprising insulin and a propellant; a metering chamber in communication with the container, the metering chamber adapted to hold a metered amount of the pharmaceutical formulation; a valve to allow the metered amount of the pharmaceutical formulation to be released from the container when the valve is actuated; and a pressurizer that applies pressure to the pharmaceutical formulation in the metering chamber while the pharmaceutical formulation is released from the metering chamber.

In another aspect of the invention, a method of aerosolizing a pharmaceutical formulation comprises containing a pharmaceutical formulation in a container, the pharmaceutical formulation comprising an active agent and a propellant; metering an amount of the pharmaceutical formulation in a metering chamber in communication with the container; releasing the pharmaceutical formulation from the metering chamber when a valve is actuated; and applying pressure within the metering chamber during the release of the pharmaceutical formulation, wherein at least 2 mg of the active agent is be aerosolized for delivery to a user during inhalation.

In another aspect of the invention, a method of aerosolizing an insulin formulation comprises containing a pharmaceutical formulation in a container, the pharmaceutical formulation comprising insulin and a propellant; metering an amount of the pharmaceutical formulation in a metering chamber in communication with the container; releasing the pharmaceutical formulation from the metering chamber when a valve is actuated; and applying pressure within the metering chamber during the release of the pharmaceutical formulation.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figures 1A and 1B are schematic sectional side views of an aerosolization device of the invention;

Figures 2A and 2B are schematic sectional side views of a version of an aerosolization device of the invention;

Figures 3A and 3B are schematic sectional side views of another version of an aerosolization device of the invention;

Figures 4A and 4B are schematic sectional side views of another version of an aerosolization device of the invention;

Figures 5A and 5B are schematic sectional side views of a version of an aerosolization device of the invention in accordance with the version of Figures 2A and 2B;

Figures 6A and 6B are schematic sectional side views of a version of an aerosolization device of the invention in accordance with the version of Figures 3A and 3B;

Figures 7A and 7B are schematic sectional side views of a version of an aerosolization device of the invention in accordance with the version of Figures 4A and 4B;

Figure 8 is a schematic sectional side view of a specific version of an aerosolization device in accordance with the version of Figures 5A and 5B;

Figure 9 is a schematic sectional side view of a specific version of an aerosolization device in accordance with the version of Figures 6A and 6B;

Figure 10 is a schematic sectional side view of a specific version of an aerosolization device in accordance with the version of Figures 7A and 7B;

Figure 11 is a schematic sectional side view of another specific version of an aerosolization device of the invention;

Figure 12 is a graph showing data obtained from experiments performed with the version of the aerosolization device shown in Figure 8.

### DESCRIPTION

The present invention relates to an aerosolization device, such as a device that uses a propellant for aerosolization, and its method of use. Although the process is illustrated in the context of aerosolizing a predetermined amount of a pharmaceutical formulation, the present invention can be used in other processes and should not be limited to the examples provided herein.

An aerosolization device **100** of the present invention is shown schematically in Figure 1A. A container **105** includes a reservoir **110** which stores a formulation, such as a pharmaceutical formulation, comprising a propellant. The formulation may further comprise an active agent dissolved in or suspended in the propellant or a mixture comprising the propellant. The propellant may comprise a superheated liquid that may be used as an atomizing energy source during actuation of the aerosolization device **100**. As shown in Figure 1A, the pharmaceutical formulation within the container **105** may include a liquid portion **115** and a gaseous portion **120** also known as a headspace.

In communication with the reservoir **110** is a metering valve **125** that is capable of allowing a metered amount of the pharmaceutical formulation to be released from the reservoir **110** in an aerosolized form. The operation of the metering valve **125** is shown in Figures 1A and 1B.

5 The metering valve **125** comprises a metering chamber **130** sized to contain a predetermined amount of the pharmaceutical formulation. A first valving mechanism **135** is moveable between an open position and a closed position. In the open position, as shown in Figure 1A, the metering chamber **130** is in communication with the reservoir **110** in the container **105** so that the pharmaceutical formulation in the reservoir **110** may flow into the metering chamber **130**. In the  
10 closed position, as shown in Figure 1B, the pharmaceutical formulation in the reservoir **130** does not flow into the metering chamber **130**. A second valving mechanism **140** is moveable between an open position, as shown in Figure 1B, and a closed position, as shown in Figure 1A. When the second valving mechanism **140** is opened, the metered amount of the pharmaceutical formulation in the metering chamber **130** is allowed to flow out of the metering chamber **130** and into an  
15 expansion chamber **145**.

The metered amount of the pharmaceutical formulation is ejected from the metering chamber **130** into the interior **150** of the expansion chamber **145** under the pressure of the flashing liquid propellant. As the propellant boils, vapor is generated to fill the void left in the metering  
20 chamber **130**. In the expansion chamber **145** the pharmaceutical formulation undergoes expansion and further boiling. As a result, the metered amount of pharmaceutical formulation is discharged through a spray orifice **155** as an aerosolized pharmaceutical formulation **160**.

In one version of the present invention, a pressurizer **165** provides additional  
25 pressure to the pharmaceutical formulation in the metering chamber **130** and/or the expansion chamber **145** during the aerosolization process. As the pharmaceutical formulation is released from the metering chamber **130**, the quantity of propellant in the metering chamber **130** decreases and the pressure generated from the boiling propellant decreases. In addition, as the propellant exits the metering chamber **130**, the expansion required to continuously fill the volume causes the  
30 propellant to cool which results in lower vapor pressures. The pressure generated from the propellant eventually becomes too low to effectively drive the pharmaceutical formulation out of

the expansion chamber **145** and through the orifice **160**. The pressurizer **165** provides additional pressure to compensate for this loss of pressure.

The added pressure from the pressurizer **165** allows for improved aerosolization of the pharmaceutical formulation. For example, in one version, the added pressure allows for a larger quantity of the pharmaceutical formulation to be aerosolized as a metered amount. Without the added pressure, the amount of pharmaceutical formulation that may be aerosolized is limited due to the dissipating energy from the reduced vapor pressure. However, with the added pressure from the pressurizer **165**, the amount of pharmaceutical formulation that may be aerosolized is unlimited. Accordingly, in one version, the aerosolization device **100** aerosolizes more than about 2 mg, preferably more than about 3 mg, and more preferably more than about 5 mg of the pharmaceutical formulation. In addition, without the added pressure, aerosolized particle size distribution for even low quantity metered amounts may be unacceptably high. However, with the aerosolization device **100**, the added pressure from the pressurizer **165** allows for small quantities of the pharmaceutical formulation to be more effectively aerosolized. For example, in one version, the aerosolization device **100** may aerosolize a metered amount containing more than about .5 mg of the pharmaceutical formulation with the aerosolized particle size distribution being acceptably low. The size of the metering chamber **130** and the amount of the pharmaceutical formulation delivered are limited only by the geometry of the device and the inhalation capabilities of a user. In one version, the volume of the metering chamber **130** may be at least about 50  $\mu\text{l}$ , preferably at least about 150  $\mu\text{l}$ , and more preferably at least about 300  $\mu\text{l}$ , and most preferably about 360  $\mu\text{l}$ . In one particular version, at least 50% of the aerosol particles generated have a diametric size of from 0.1  $\mu\text{m}$  to 10  $\mu\text{m}$ , more preferably from 1  $\mu\text{m}$  to 5  $\mu\text{m}$ . Even more preferably at least about 80% of the aerosolized particles are within the desired size ranges.

In one version, the pressurizer **165** may comprise a mechanism that changes the volume of the metering chamber **130**. Since pressure is related to volume, by decreasing the volume of the metering chamber **130**, the pressure in the chamber is increased. For example, as shown in Figures 2A and 2B, the pressurizer **165** comprises a moveable member, such as a plunger **170**. A force **175** may be applied to the plunger during the aerosolization process so that the pressure in the metering chamber **130** does not dissipate as rapidly as it would in a constant volume



metering chamber. The force **175** may be constant or may vary. In one version, the force **175** is constant and substantially equal to the force acting on the plunger **170** by the pressurized gas in the filling position of Figure 2A so that a substantially constant pressure is applied for at least a period of time during the aerosolization process of Figure 2B. In another version, the force **175** is slightly less than the force acting on the plunger **170** by the pressurized pharmaceutical formulation in the filling position of Figure 2A. In this version, when in the filling position of Figure 2A, the force acting on the plunger **170** from the pressurized pharmaceutical formulation is sufficient to move the plunger **170** to the retracted position shown in Figure 2A.

Alternatively or additionally, the pressurizer **165** may change the volume of the metering chamber **130** by providing the metering chamber **130** with one or more flexible walls **180**, as shown for example in Figures 3A and 3B. For example, the flexible wall **180** may be composed of a flexible polymeric or natural material. A force **185** may act on the wall **180** to cause the wall **180** to collapse and thereby decrease the volume of the metering chamber **130**. The magnitude of the force **185** may be similar to that discussed above in connection with Figure 2A and 2B. In one version, the wall **180** may be biased into the position shown in Figure 3A to allow the metering chamber **130** to be filled with the metered amount of pharmaceutical formulation during the filling process. In another version, the pressure of the pharmaceutical formulation may be greater than the force **185** to cause the wall **180** to expand to configuration shown in Figure 3A. During the aerosolization process shown in Figure 3B, the force **185** causes the metering chamber **130** to decrease in volume to add pressure to the metering chamber **130**.

In another version, the pressurizer **165** uses pressurized gas to add pressure to the metering chamber **130**. For example, as shown in the version of Figures 4A and 4B, the pressurizer **165** may comprise a source of pressurized gas **190** that is capable of communicating with the metering chamber **130**. A third valving mechanism **195** is provided to control the application of the pressurized gas to the metering chamber **130**. During the metering chamber filling process of Figure 4A, the third valving mechanism **195** is closed to allow the metering chamber **130** to fill with the pharmaceutical formulation from the reservoir **110** in the container **105**. During the aerosolization process shown in Figure 4B, the third valving mechanism **195** is opened to allow the pressurized gas to flow into the metering chamber **130** to increase the pressure

therein. In one version, the third valving mechanism **195** is returned to the closed position after a period of time to prevent excessive loss of the pressurized gas through the orifice **155**.

Accordingly, in this version the pressurizer **165** provides a burst of pressurized gas to the metering chamber **130** when the pharmaceutical formulation is being emptied from the metering chamber **130**.

In particularly useful versions of the present invention, the metering valve **125** may be at least partially within the container **105**. When the metering valve **125** is provided at least partially in the container **105**, the pressurized pharmaceutical formulation may be used to supply the energy for the pressurizer **165**. Thus, the need for an addition force applicator or source of pressurized gas is eliminated.

Figures 5A and 5B show a version of an aerosolization device **100** similar to the version of Figures 2A and 2B, but with at least a portion of the metering valve **125** being within the container **105**. In this version, the pressurizer **165** comprises a plunger **170** that is moveable within the metering chamber **130** to reduce the volume of the metering chamber **130** during pharmaceutical formulation aerosolization. In the filling position shown in Figure 5A, the pharmaceutical formulation is allowed to flow from the reservoir **110** into the metering chamber **130**. The plunger **170** separates the metering chamber **130** from the reservoir **110**. One side of the plunger **170** is acted on by the pressure within the metering chamber **130** and another side of the plunger **170** is acted on by the pressure within the reservoir. In the Figure 5A condition, the first valving mechanism **135** is open and there is equilibrium between the metering chamber **130** and the reservoir **110**. Accordingly, the plunger **170** does not move. When the aerosolization device **100** is actuated to cause the metered amount of the pharmaceutical formulation to be aerosolized, as shown in Figure 5B, the pressure within the metering chamber **130** begins to decrease, as discussed above. As a result, the pressure from the reservoir **110** is greater than the pressure from the metering chamber **130** and the plunger **170** is caused to move as shown to reduce the volume of the metering chamber **130** and to reduce the decrease in pressure in the metering chamber **130**. A biasing member, such as a spring (not shown) may also be provided to return the plunger to the retracted position shown in Figure 5A when the aerosolization process is completed and the metering chamber **130** is to be filled again.

In like manner, the version of Figures 6A and 6B are similar to the version of Figures 3A and 3B with at least a portion of the metering valve **125** being within the container **105**. In this version, the pressurizer **165** comprises a flexible wall **180** on the metering chamber **130**, and the pressurized pharmaceutical formulation within the reservoir **110** acts on the flexible wall **180** of the metering chamber **130** to cause the metering chamber **130** to have a reduced volume during the aerosolization process, as shown in Figure 6B. The flexible wall **180** may be biased into its expanded position shown in Figure 6A to allow the metered amount of the pharmaceutical to enter into the metering chamber **130**. Upon actuation and during aerosolization, as shown in Figure 6B, the pressure in the reservoir **110** is greater than the pressure in the metering chamber **130** and the wall **180** of the metering chamber moves so as to reduce the volume in the metering chamber **130**.

In the version of Figures 7A and 7B, the pressurizer **165** comprises an arrangement that allows pressurized gas to be introduced into the metering chamber during the aerosolization process, as in the version of Figures 4A and 4B. However, in the version of Figures 7A and 7B, the source of pressurized gas **190** is the gaseous component **120** in the reservoir **110** of the container **105**. The pressurizer **165** in this version comprises a conduit **205** that extends into the gaseous portion **120** and which allows the gaseous portion **120** to communicate with the metering chamber **130** when the third valving mechanism **195** is open.

Figure 8 shows a specific version of a metering valve **125** comprising a pressurizer **165**. The metering valve **125** is positioned within the reservoir **110** of a container **105** containing a pharmaceutical formulation comprising a propellant. Figure 8 shows the metering valve **125** in its filling position. The pharmaceutical formulation flows through an opening into the metering chamber **130**. In a portion **215** of the metering chamber **130** a plunger is moveably positioned. One side **220** of the plunger is acted on by the pressure in the metering chamber **130**. Another side **225** of the plunger is acted on by pressure in the reservoir **110**. When in the filling position, the first valving mechanism **135** is open and the pressure in the metering chamber **130** is the same as the pressure in the reservoir **110**. A biasing member **230** biases the plunger **170** to the position shown in Figure 8. The metering valve **125** comprises a moveable stem **235**. The stem **235** is biased into the position shown in Figure 8 by a spring **240**. Movement of the stem **235** to compress

the spring **240** causes actuation of the aerosolization device **100** which results in aerosolization of the pharmaceutical formulation contained within the metering chamber **130**. This movement of the stem **235** causes the first valving mechanism **135** to close by causing a portion **245** of the stem to block the opening **210** into the metering chamber **130**. Simultaneously or shortly thereafter upon continued movement of the stem **235**, the second valving member **140** is opened by causing an opening **250** into the interior **150** of the expansion chamber **145** to be in communication with the metering chamber **130**. The pharmaceutical formulation in the metering chamber **130** is then ejected into the expansion chamber **145**, as discussed above. As the pressure in the metering chamber **130** is reduced, the pressure difference on the plunger **170** becomes sufficiently large to overcome the force of the biasing member **230** thereby causing the plunger to move **170** to decrease the volume of the metering chamber **130**. After actuation and aerosolization, the spring **240** returns the stem **235** to the position shown in Figure 8 and as the pressure in the metering chamber **130** and in the reservoir equilibrate, the biasing member **230** returns the plunger to its extended position so that the aerosolization device **100** is again armed for actuation.

Other pressurizer **165** versions may also be used with the stem actuator. For example, Figure 9 shows a specific version of a metering valve **125** comprising a pressurizer **165** having a flexible wall **180** of the type described above in connection with the version of Figures 3A and 3B and with the version of Figures 6A and 6B. The flexible wall **180** is shown in its extended position in Figure 9 where it defines the volume of the metering chamber **130**. During actuation of the aerosolization device **100** by moving the stem **235** as described above, the flexible wall **180** collapses under the force of the pressure in the reservoir **110** to reduce the volume of the metering chamber **130**. A biasing mechanism, such as a leaf spring, may be provided to cause the flexible wall **180** to move to the extended position shown in Figure 9.

In another exemplary version, Figure 10 shows a version of a metering valve **125** having a pressurizer **165** that introduces pressurized gas into the metering chamber **130** during actuation, as described above in connection with Figures 7A and 7B. The conduit **205** that extends to the gaseous portion **120** in the container **105** is connected to and extends partially through the stem **235**. The third valving mechanism **195** is operated by movement of the stem **235**. The third valving mechanism **195** comprises a lower end **251** of the conduit **205** and a wall **255** of the

metering chamber **130**. In Figure 10, the third valving mechanism **195** is in its closed position which is provided by the end **251** of the conduit **205** being blocked by the wall **255** of the metering chamber **130**. As the stem **235** moves upward, the end **205** also moves upward until it reaches a portion **260** of the metering chamber where the end **250** does not contact the wall **255**. At this position, the metering chamber **130** is in communication with the gaseous portion **120** and the pressurized gas is introduced into the metering chamber **130** to increase the pressure therein. In one version, the portion **260** is sufficiently small that the third valving mechanism **195** is open only for a period of the actuation process so that a burst of pressurized gas is introduced.

Figure 11 shows another version of an aerosolization device **100** having a metering valve **125** with a pressurizer **165** that comprises a bi-stable member **280**. For example, the bi-stable member **280** may be in the form of a bistable dome that is stable in at least two positions, such as the dome configuration shown in Figure 11 in solid lines and in an inverted configuration **285** shown in broken lines. In this version, the bi-stable member **280** assumes the dome configuration when the pressure on the interior **290** is substantially the same as the pressure on the exterior **295**. The bi-stable member then moves to the inverted configuration **285** when the exterior pressure exceeds the interior pressure. Figure 11 shows the metering valve in the filling position. In this position, the pharmaceutical formulation within the reservoir **110** of the container **105** passes through an opening **305** and into the metering chamber volume **130** that includes the interior **290** of the bi-stable member **280**. When the metering valve **125** is actuated by moving the valve stem **235** upwardly, the top of the stem **310** contacts a sealing member **315** to close the metering chamber **130** from the reservoir **110**. As the stem **235** continues to move upwardly, an opening **320** into the metering chamber **130** and the opening **250** into the interior **150** of the expansion chamber **145** are in communication so that the metered volume of the pharmaceutical formulation may be aerosolized, as discussed above. During the aerosolization process, the pressure is lowered in the metering chamber **130**. This causes the bi-stable member **280** to invert to the inverted position **285**, thereby decreasing the volume of the metering chamber **130** and increasing the pressure therein when compared to metering chamber that maintains a constant volume. For the sake of clarity, the return spring **240** that returns the stem **235** to its filling position is not shown in the figure.

Figure 12 shows data obtained from experiments performed with the version of the aerosolization device shown in Figure 8. The graph shows expansion chamber pressure using an HFA propellant. Two tests were performed with the metering chamber volume held constant. The resulting curves are shown at 370. In addition, four tests were performed with the volume of the metering chamber being reduced by the movement of the plunger during actuation. These variable volume curves are shown at 375. As can be seen, the pressurizer 165 of the present invention allows for a longer aerosolization period and correspondingly allows for a larger amount of the pharmaceutical formulation to be aerosolized.

The reservoir 110 may be in a canister in which a pharmaceutical formulation is stored in or with a propellant, such as a hydrofluoroalkane, as discussed in U.S. Patent 5,225,183; U.S. Patent 5,681,545; U.S. Patent 5,683,677; U.S. Patent 5,474,759; U.S. Patent 5,508,023; U.S. Patent 6,309,623 and in U.S. Patent 5,655,520 all of which are incorporated herein by reference in their entireties. Propellant based metered dose inhalers may employ a dry powdered pharmaceutical formulation which is suspended or dissolved in a liquefied gas propellant. The pharmaceutical formulation may further comprise one or more excipients or surfactants to aid in the suspension and/or in the solubility, as discussed in the above-listed patents. After actuation, the propellant evaporates almost immediately leaving a fine dry powder.

In a preferred version, the invention provides a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves,

adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxidants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent

No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosphonates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyribonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiramycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxacin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymyxins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicillinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalixin, cephradine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone dipropionate, triamcinolone acetamide, budesonide acetone, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the



above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

5           Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk  
10   Reference (most recent edition).

          The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its  
15   activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also depend upon the relative amounts of additives contained in the composition. The compositions of  
20   the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

25           The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which  
30   are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably

from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight.

Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperatures ( $T_g$ ) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility- enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrans (e.g., cyclodextrins, such as 2-hydroxypropyl- $\beta$ -cyclodextrin and sulfobutylether- $\beta$ -cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19<sup>th</sup> ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52<sup>nd</sup> ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

The pharmaceutical formulation may also be treated so that it has high stability. Several attempts have dealt with improving suspension stability by increasing the solubility of

surface-active agents in the HFA propellants. To this end U.S. Pat. No. 5,118,494, WO 91/11173 and WO 92/00107 disclose the use of HFA soluble fluorinated surfactants to improve suspension stability. Mixtures of HFA propellants with other perfluorinated cosolvents have also been disclosed as in WO 91/04011. Other attempts at stabilization involved the inclusion of nonfluorinated surfactants. In this respect, U.S. Pat. No. 5,492,688 discloses that some hydrophilic surfactants (with a hydrophilic/lipophilic balance greater than or equal to 9.6) have sufficient solubility in HFAs to stabilize medicament suspensions. Increases in the solubility of conventional nonfluorinated MDI surfactants (e.g. oleic acid, lecithin) can also reportedly be achieved with the use of co-solvents such as alcohols, as set forth in U.S. Pat. Nos. 5,683,677 and 5,605,674, as well as in WO 95/17195. Unfortunately, as with the prior art cosolvent systems previously discussed, merely increasing the repulsion between particles has not proved to be a very effective stabilizing mechanism in nonaqueous dispersions, such as MDI preparations. All of the aforementioned references being incorporated herein by reference in their entireties.

“Mass median diameter” or “MMD” is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. “Mass median aerodynamic diameter” or “MMAD” is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10  $\mu\text{m}$  mass median diameter (MMD), preferably less than 7.5  $\mu\text{m}$ , and most preferably less than 5  $\mu\text{m}$ , and usually being in the range of 0.1  $\mu\text{m}$  to 5  $\mu\text{m}$  in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the aerosol particle

size distribution is about 1.0 - 5.0  $\mu\text{m}$  mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5  $\mu\text{m}$  MMAD and preferably 1.5 - 4.0  $\mu\text{m}$  MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties.

In one particular example, the pharmaceutical formulation comprises insulin. Example of suitable suspension or solution insulin formulations can be found in U.S. Patent 5,006,343; U.S. Patent 5,364,838; U.S. Patent 6,432,383; U.S. Patent 6,540,982, all of which are incorporated herein by reference in their entireties. A particularly useful formulation of insulin comprises insulin in a phospholipid matrix, as disclosed in U.S. Patent 6,433,040 and suspended in an HFA propellant as described in U.S. Patent 6,309,623, both of which are incorporated herein by reference in their entireties. The advantage of aerosolizing the insulin formulations using the aerosolization device **100** of the present invention is that large and/or uniform doses can be generated that are not possible to generate in conventional meter dose inhalers. For example, at least a 2 mg dose of insulin can be administered using the above formulations in combination with an aerosolization device **100** of the present invention. In other versions, at least 3 mg and at least 5 mg of insulin can be aerosolized for delivery to a patient in need of insulin.

A capture chamber may be provided in certain applications. Suitable capture chambers are disclosed in U.S. Patent 5,458,135; U.S. Patent 5,740,794; U.S. Patent 6,257,233; and U.S. Patent 4,534,343, all of which are incorporated herein by reference in their entireties. The capture chamber may be useful when a user is unable to coordinate his or her inhalation with the actuation of the aerosolization device **100** or when the dose is sufficiently large that it is aerosolized in a manner than causes a stream of medicament to impact the back of a user's throat during use.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the relative positions of the elements in

the aerosolization device may be changed, and flexible parts may be replaced by more rigid parts that are hinged, or otherwise movable, to mimic the action of the flexible part. In addition, the passageways need not necessarily be substantially linear, as shown in the drawings, but may be curved or angled, for example. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.